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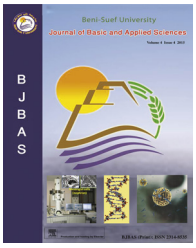

Full Length Article

Synthesis and preliminary antimicrobial evaluation of some new 6-methoxyquinoline-3-carbonitrile derivatives

Mohamed Hagrs [a], *Ashraf H. Bayoumi* [a], *Kamal M. El-Gamal* [a,b], *Abdelrahman S. Mayhoub* [a], *Hamada S. Abulkhair* [a,*]

[a] *Organic Chemistry Department, Faculty of Pharmacy, Al-Azhar University, Nasr City 11884, Egypt*

[b] *Pharmaceutical Organic Chemistry Department, Faculty of Pharmacy, Delta University for Science and Technology, Mansoura, Egypt*

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ABSTRACT

A series of new 6-methoxyquinoline-3-carbonitrile derivatives were synthesized using a variety of synthetic routes. The newly synthesized compounds have been characterized by IR, ^{1}H NMR, and mass spectral data followed by elemental analysis. All of the synthesized compounds were evaluated for their in-vitro antimicrobial activity against *Streptococcus pneumonia* and *Bacillus subtilis* as examples for Gram-positive bacteria, *Pseudomonas aeruginosa* and *Escherichia coli* as examples for Gram-negative bacteria, and *Aspergillus fumigatus*, *Syncephalastrum racemosum*, *Geotriucum candidum* and *Candida albicans* as representative examples of fungi. The majority of tested compounds showed moderate activities against wide range of selected organisms. Among the tested compounds, the ester derivative **7b** and the thioether derivative **9c** showed the highest antimicrobial activity against gram-positive strains while the highest activity against gram-negative strains was observed in case of **7b**, **7d** and **9b** while compound **7e** found more active than Amphotericin B against three fungal species.

1. Introduction

The discovery and development of antimicrobial agents that has met with enormous success over the past 50 years provided many classes of natural products and synthetic compounds. Among them, quinoline derivatives are still an important class of therapeutically useful antibacterial drugs (Agui et al., 1977; Kharb and Kaur, 2013). Additionally, infections caused by microbes thus far not considered as pathogens in the normal host have become a challenging problem in the past decade, due to an increase in the number of elderly patients, new medical techniques such as implantable devices, and patients suffering from severe immunosuppression that necessitates requiring continuous search into novel classes of antibacterial agents (Bonatti et al., 2003). At least in the United

* *Corresponding author.* Organic Chemistry Department, Faculty of Pharmacy, Al-Azhar University, Nasr City 11884, Egypt. Tel.: +20225620405.
E-mail address: hamadaorganic@azhar.edu.eg (H.S. Abulkhair).

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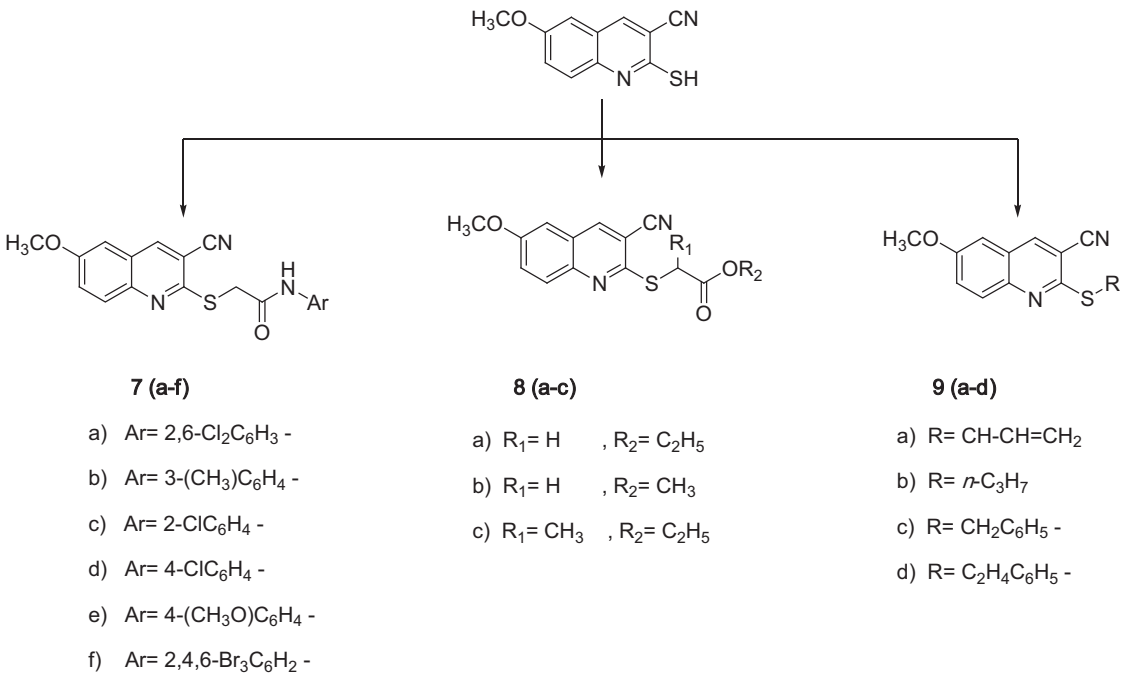


Fig. 1 – Graphical abstract of the newly synthesized 6-methoxyquinoline-3-carbonitrile derivatives.

States, deaths caused by a single multi-resistant species, MRSA, might be more than those caused by AIDS (Anibal et al., 2010). The aim of this work is to develop a new set of antibacterial agents belonging to quinoline scaffold that cannot be recognized by bacterial resistant machineries (Fig. 1). Structurally related quinoline analogues have been well-known a long time ago, but cross-resistance has not been reported yet. As previously mentioned some heterocyclic compounds containing 2-chloroquinolne-3-carbaldehyde moiety have been documented as antimicrobial agents (Burckhalter et al., 1961; Dow et al., 2004). Some of the recently modified quinolines (Fig. 2) include Bedaquiline, which has shown extraordinary activity against both drug susceptible and drug-resistant strains of *Mycobacterium tuberculosis* (Diacon et al., 2009). Laquinimod is a quinoline derivative currently under investigation for oral treatment of multiple sclerosis (MS) (Haggiag et al., 2013). Glaxo-SmithKline 299423 is an investigational quinoline derivative that has shown potent activity against antibiotic-resistant strains of bacteria such as *Staphylococus aureus*, including methicillin resistance strains (MRSA) and gram-negative bacteria like *Escherichia coli* (Bax et al., 2010). In this study, Glaxo-SmithKline 299423 (**3**) was used as lead compound with modification at position 2 by introducing different functional groups like amide, ester and thioether aiming to obtain active antimicrobial compounds. Depending on the above-mentioned facts, and for further investigation of novel antimicrobial agents, the global aim of the current work was designed to synthesize some new derivatives of 6-methoxyquinoline-3-carbonitriles, which showed promising antimicrobial activity.

2. Experimentals

2.1. *General*

All melting points were determined by open capillary using Gallenkamp melting point apparatus and are uncorrected. The IR spectra (in KBr discs) were recorded on potassium bromide discs on a Pye Unicam SP 3300 spectrophotometer. ^{1}H NMR spectra were recorded on Gemini 300 MHz using TMS as an internal standard. All chemical shifts are reported in ppm downfield from TMS. Mass spectra were recorded on a Shimadzu GCMS-QP 1000 EX mass spectrometer operating at 70 eV. Elemental analyses were carried out at the Regional Center for Mycology and Biotechnology, Al-Azhar University, Cairo, Egypt. Progress of the reactions was monitored by TLC sheets precoated

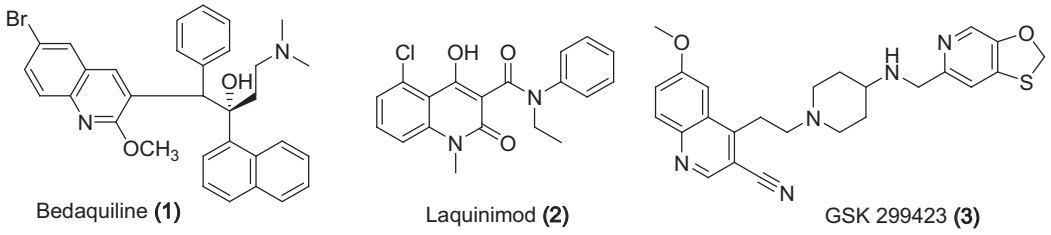
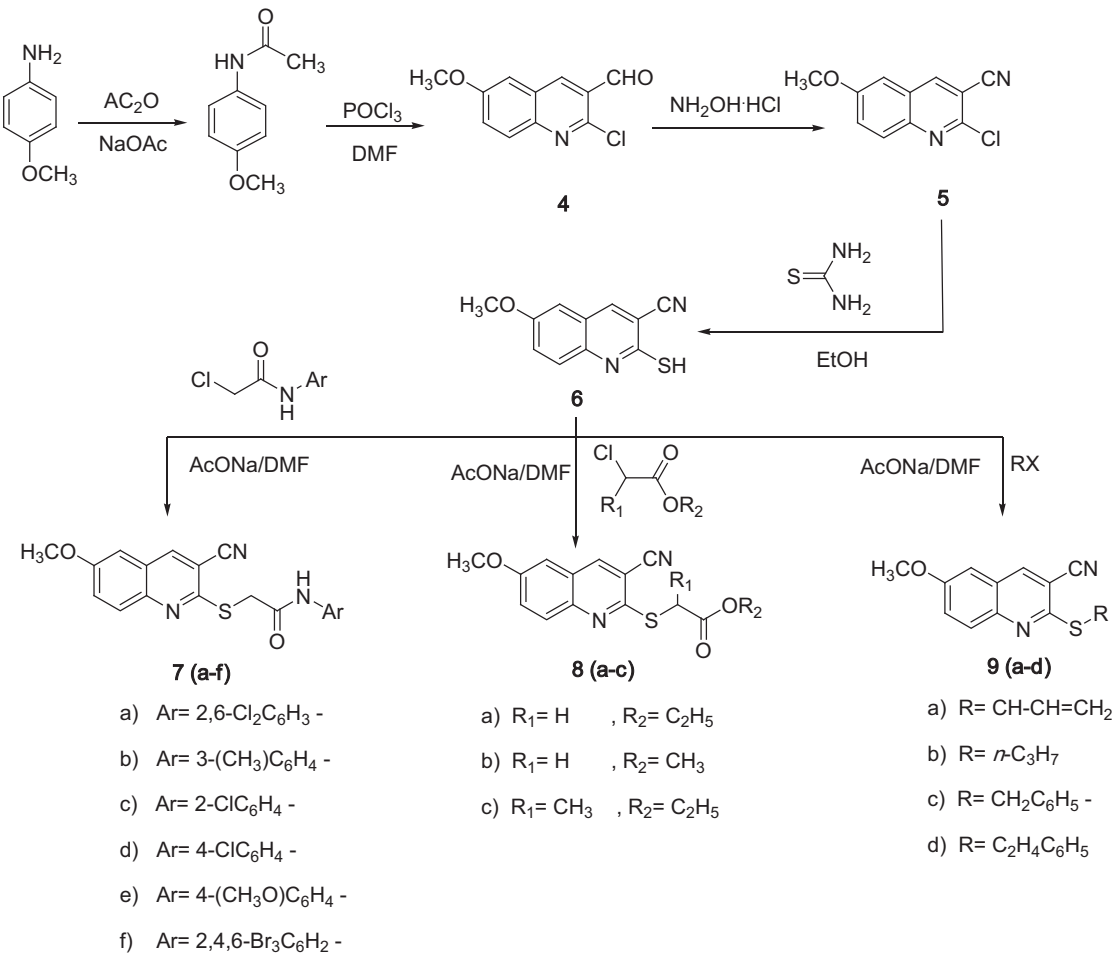


Fig. 2 – Chemical structures of some potent antimicrobial quinoline derivatives.



Scheme 1 – Synthetic protocol for compounds 7a–f**,** 8a–c **and** 8a–d**.**

with UV fluorescent silica gel Merck 60 F254 plates and were visualized using UV lamp and n-hexane:ethyl acetate 9:1 as mobile phase. Starting materials were purchased from Aldrich Chemical Company and used without further purification. Compound **4** was prepared according to reported procedure (Rajakumar and Raja, 2015; Venkatesan and Sumathi, 2010) by applying Vilsmeier–Haack reaction of phosphorus oxytrichloride, *N*,*N*-dimethylformamide with *N*-(4-anisyl)acetamide. 2-Chloro-6-methoxyquinoline-3-carbonitrile (**5**) was obtained following literature procedures (Augustine et al., 2009; Upadhya et al., 2009). 2-Mercapto-6-methoxyquinoline-3-carbonitrile (**6**) was prepared by reacting 2-chloro-6-methoxyquinoline-3-carbonitrile **5** with thiourea in dry ethanol (Nandeshwarappa et al., 2006; Prakash et al., 2009). For synthesis of the new derivatives, Scheme 1 was adopted.

2.2. *General procedure for synthesis of 2-(3-Cyano-6-methoxyquinolin-2-ylthio)-N-(aryl)acetamides 7a–f*

A mixture of compound **6** (2.16 g, 10 mmol) and the appropriate chloroacetanilide (10 mmol) in DMF (20 mL) containing anhydrous sodium acetate (1.23 g, 15 mmol) was heated over water bath for 3 hours. The reaction mixture was then cooled, poured into ice-cooled water (200 mL), and stirred well for 30 min. The solid thus separated was filtered, washed with water, dried, and crystallized from ethanol to obtain compounds **7a–f** as white needles.

2.2.1. *2-(3-Cyano-6-methoxyquinolin-2-ylthio)-N-(2,6-dichlorophenyl)acetamide (7a)*

Yield (3.55 g, 85%); mp 250–251 °C; IR (KBr) υ_{max}/cm^{-1}; 3288 (NH), 3032 (C-H aromatic), 2957 (CH aliphatic), 2220 (C≡N) and 1655 (C═O); ^{1}H NMR (DMSO): 10.29 (s, 1H, NH, D_2O exchangeable), 9.0 (s, 1H, Quinoline H4), 7.7 (d, 1H, *J* = 9 Hz, Quinoline H8), 7.6 (d, 2H, *J* = 6 Hz, phenyl H3, H5), 7.5 (d, 1H, *J* = 9 Hz, Quinoline H7), 7.4 (t, 1H, *J* = 6 Hz, phenyl H4) 7.3 (s, 1H, Quinoline H5), 4.36 (s, 2H, S-CH_2), and 3.95 (s, 3H, OCH_3); MS (m/z, %); 418 (M, 1.94%), 257 (M – $NHC_6H_3Cl_2$, 100%) and 229 (M – $NHC_6H_3Cl_2$ – CN, 64.05%); Anal. Calcd for $C_{19}H_{13}C_{l2}N_3O_2S$, (418): C, 65.61; H, 5.82; N, 4.28%. Found: C, 65.64; H, 5.87; N, 4.32%.

2.2.2. *2-(3-cyano-6-methoxyquinolin-2-ylthio)-N-m-tolylacetamide (7b)*

Yield (3.09 g, 85%); mp 222–223 °C; IR (KBr) υ_{max}/cm^{-1}; 3300 (NH), 3031 (CH aromatic), 2900 (CH aliphatic), 2221 (C≡N), 1665 (C═O); ^{1}H NMR (DMSO): 10.42 (s, 1H, NH, D_2O exchangeable), 8.87 (s, 1H, quinoline H4), 7.8 (d, 1H, *J* = 9.6 Hz, quinoline H8), 7.6 (d, 1H, *J* = 9.6 Hz, Quinoline H7), 7.5 (s, 1H, phenyl H2), 7.4 (s, 1H, quinoline H5), 7.3 (d, 1H, *J* = 7.8 Hz, phenyl H6), 7.2 (t, 1H, *J* = 15 Hz, phenyl H5), 6.8 (d, 1H, *J* = 6 Hz, phenyl H4), 4.2 (s, 2H, S-CH_2),

3.95 (s, 3H, OCH_3), 2.6 (s, 3H, CH_3); MS (m/z, %); 363 (M, 9.34%), 257 (M – $NHC_6H_4CH_3$, 100%), 229 (M – $NHC_6H_4CH_3$ – CN, 75.70%) and 107 ($NHC_6H_4CH_3$, 44.60%); Anal. Calcd for $C_{20}H_{17}N_3O_2S$, (363): C, 66.10; H, 4.71; N, 11.56%. Found: C, 66.21; H, 4.69; N, 11.61%.

2.2.3. 2-(3-Cyano-6-methoxyquinolin-2-ylthio)-N-(2-chlorophenyl)acetamide (7c)

Yield (3.07, 80%); mp 239–240 °C; IR (KBr) υ_{max}/cm^{-1}; 3295 (NH), 3080 (CH aromatic), 2900 (CH aliphatic), 2222 (C≡N), 1675 (C═O); ^1H NMR (DMSO): 10.1 (s, 1H, NH, D_2O exchangeable), 9.0 (s, 1H, Quinoline H4), 7.8 (d, 1H, *J* = 9 Hz, Quinoline H8), 7.6 (d, 1H, *J* = 9 Hz, Quinoline H7), 7.5 (d, 2H, *J* = 18 Hz, phenyl H3, H6), 6.8 (t, 2H, *J* = 18, phenyl H4, H5), 7.4 (s, 1H, Quinoline H5), 4.35 (s, 2H, S-CH_2), 3.95 (s, 3H, OCH_3); MS (m/z, %); 383 (M, 1.42%), 257 (M – NHC_6H_4Cl, 100%) and 229 (M – NHC_6H_4Cl – CN, 73.51%); Anal. Calcd for $C_{19}H_{14}ClN_3O_2S$, (383): C, 59.45; H, 3.68; N, 10.95%. Found: C, 59.62; H, 3.65; N, 11.21%.

2.2.4. 2-(3-Cyano-6-methoxyquinolin-2-ylthio)-N-(4-chlorophenyl)acetamide (7d)

Yield (3.07, 80%); mp 239–240 °C; IR (KBr) υ_{max}/cm^{-1}; 3296 (NH), 3082 (CH aromatic), 2905 (CH aliphatic), 2221 (C≡N), 1674 (C═O); ^1H NMR (DMSO): 10.1 (s, 1H, N-H, D_2O exchangeable), 9.0 (s, 1H, Quinoline H4), 7.8 (d, 1H, *J* = 9 Hz, Quinoline H8), 7.6 (d, 1H, *J* = 9 Hz, Quinoline H7), 7.4 (s, 1H, Quinoline H5), 6.8–7.0 (2d, 4H, *J* = 18 Hz, Phenyl H 2, 3, 5 and 6), 4.35 (s, 2H, S-CH_2) and 3.95 (s, 3H, OCH_3); MS (m/z, %); 383 (M, 0.87%), 257 (M – NHC_6H_4Cl, 100%) and 229 (M – NHC_6H_4Cl – CN, 90.46%); Anal. Calcd for $C_{19}H_{14}ClN_3O_2S$, (383): C, 59.45; H, 3.68; N, 10.95%. Found: C, 59.62; H, 3.65; N, 11.21%.

2.2.5. 2-(3-Cyano-6-methoxyquinolin-2-ylthio)-N-(4-methoxyphenyl) acetamide (7e)

Yield (3.22 g, 85%); mp 230–231 °C; IR (KBr) υ_{max}/cm^{-1}; 3261 (NH), 3071 (CH aromatic), 2910 (CH aliphatic), 2225 (C≡N), 1666 (C═O); ^1H NMR (DMSO): 10.29 (s, 1H, NH, D_2O exchangeable), 9.0 (s, 1H, Quinoline H4), 7.8 (d, 1H, *J* = 9 Hz, Quinoline H8), 7.6 (d, 1H, *J* = 9 Hz, Quinoline H7), 7.5 (d, 2H, *J* = 18 Hz, phenyl H2, 6), 7.4 (s, 1H, Quinoline H5), 6.8 (d, 2H, *J* = 18, phenyl H3, 5), 4.2 (s, 2H, SCH_2), 3.95 (s, 3H, Quinoline OCH_3) and 3.7 (s, 3H, phenyl OCH_3); MS (m/z, %); 379 (M, 2.90%), 257 (M – $NHC_6H_4OCH_3$, 29.90%) and 229 (M – $NHC_6H_4OCH_3$ – CN, 100%); Anal. Calcd for $C_{20}H_{17}N_3O_3S$, (379): C, 63.31; H, 4.52; N, 11.07 %. Found: C, 63.62; H, 4.6; N, 11.35%.

2.2.6. 2-(3-Cyano-6-methoxyquinolin-2-ylthio)-N-(2,4,6-tribromophenyl)acetamide (7f)

Yield (4.37 g, 75%); mp 270–271 °C; IR (KBr) υ_{max}/cm^{-1}; 3321 (NH), 3026 (CH aromatic), 2925 (CH aliphatic), 2222 (C≡N), 1670 (C═O); ^1H NMR (DMSO): 10.29 (s, 1H, NH, D_2O exchangeable), 9.0 (s, 1H, quinoline-H4), 7.8 (d, 1H, *J* = 9 Hz, quinoline H8), 7.7 (s, 2H, phenyl-H3, H5), 7.6 (d, 1H, *J* = 9 Hz, quinoline H7), 7.4 (s, 1H, quinoline H5), 4.3 (s, 2H, S-CH_2) and 3.95 (s, 3H, OCH_3); MS (m/z, %); 418 (M, 1.94%), 257 (M – $NHC_6H_2Br_3$, 63.33%) and 230 (M – $CONHC_6H_2Br_3$, 100%); Anal. Calcd for $C_{19}H_{12}Br_3N_3O_2S$, (583): C, 38.94; H, 2.06; N, 7.17%. Found: C, 39.29; H, 2.03; N, 7.29%.

2.3. General procedure for synthesis of alkyl-2-(3-cyano-6-methoxyquinolin-2-ylthio)alkanoates 8a–c

A mixture of **6** (2.16 g, 10 mmol) and the appropriate alkyl chloroacetate or chloropropionate (10 mmol) in DMF (20 ml) containing anhydrous sodium acetate (1.23 g, 15 mmol) was heated on a water-bath with continuous stirring for 6 h, the solid so obtained was filtered, dried and crystallized from ethanol to afford the corresponding ester derivatives **8a–c** as white needles.

2.3.1. Ethyl 2-(3-cyano-6-methoxyquinolin-2-ylthio)acetate (8a)

Yield (2.14 g, 80%); mp 135–136 °C; IR (KBr) υ_{max}/cm^{-1}; 3060 (CH aromatic), 2970 (CH aliphatic), 2222 (C≡N) and 1719 (C═O); ^1H NMR (DMSO): 9.0 (s, 1H, Quinoline H4), 7.9 (d, 1H, *J* = 9 Hz, quinoline H8), 7.5 (d, 1H, *J* = 9 Hz, quinoline H7), 7.4 (s, 1H, quinoline H-5), 4.6 (s, 2H, S-CH_2), 4.3 (q, 2H, *J* = 21 Hz, O-CH_2), 3.9 (s, 3H, O-CH_3) and 1.3 (t, 3H, *J* = 15 Hz, CH_2-**CH_3**); MS (m/z, %); 302 ($C_{15}H_{14}N_2O_3S$, 9%, M), 257 (M – OC_2H_5, 5.3%), 229 (M – OC_2H_5 – CN, 100%), 214 (M – $CH_2COOC_2H_5$, 5.4%); Anal. Calcd for $C_{15}H_{14}N_2O_3S$, (302): C, 59.59; H, 4.67; N, 9.27%. Found: C, 59.12; H, 4.29; N, 9.70%.

2.3.2. Methyl 2-(3-cyano-6-methoxyquinolin-2-ylthio)acetate (8b)

Yield (2.38 g, 85%); mp 141–142 °C; IR (KBr) υ_{max}/cm^{-1}; 3069 (CH aromatic), 2948 (CH aliphatic), 2220 (C≡N) and 1731 (C═O); ^1H NMR (DMSO): 9.0 (s, 1H, quinoline H4), 7.9 (d, 1H, *J* = 9 Hz, quinoline H8), 7.5 (d, 1H, *J* = 9 Hz, quinoline H7), 7.4 (s, 1H, quinoline H5), 4.2 (s, 2H, SCH_2), 3.9 (s, 3H, O-CH_3), 3.6 (s, 3H, COO-CH_3); MS (m/z, %); 288 (M, 100%), 257 (M – OCH_3, 20%), 229 (M – OCH_3 – CN, 99%); Anal. Calcd for $C_{14}H_{12}N_2O_3S$, (288): C, 58.32; H, 4.20; N, 9.72%. Found: C, 58.43; H, 4.27; N, 9.88%.

2.3.3. Ethyl 2-(3-cyano-6-methoxyquinolin-2-ylthio)propanoate (8c)

Yield (2.68 g, 85%); mp 160–161 °C; IR (KBr) υ_{max}/cm^{-1}; 3052 (CH aromatic), 2926 (CH aliphatic), 2222 (C≡N) and 1735 (C═O); ^1H NMR (DMSO): 9.0 (s, 1H, quinoline H4), 7.9 (d, 1H, *J* = 9 Hz, quinoline H8), 7.5 (d, 1H, *J* = 9 Hz, quinoline H7), 7.4 (s, 1H, quinoline H5), 4.6 (q, 1H, *J* = 12 Hz, S-CH), 4.1 (q, 2H, *J* = 10.8 Hz, OCH_2), 3.9 (s, 3H, OCH_3), 1.6 (d, 3H, *J* = 12 Hz, $SCHCH_3$), 1.1 (t, 3H, *J* = 15 Hz, CH_2CH_3); MS (m/z, %); 316 (M, 100%), 257 (M – OCH_3, 20%), 229 (M – OCH_3 – CN, 99%); Anal. Calcd for $C_{16}H_{16}N_2O_3S$, (316): C, 60.74; H, 5.10; N, 8.85%. Found: C, 60.83; H, 5.02; N, 8.97%.

2.4. General procedure for synthesis of 6-methoxy-2-(alkyl or aralkylthio)quinoline-3-carbonitrile 9a–d

Into a suspension of 2-mercapto-6-methoxyquinoline-3-carbonitrile **(6)** (2.16 g, 10 mmol) and anhydrous sodium acetate (1.23 g, 15 mmol) in ethanol (30 ml), the appropriate alkyl or aralkylhalide (10 mmol) was added. The reaction mixture was refluxed for 2 hours. On cooling, the resulting precipitate was collected and recrystallized from ethanol in the form of white needles.

2.4.1. 2-(Allylthio)-6-methoxyquinoline-3-carbonitrile (9a)

Yield (2.20 g, 86%); mp 115–116 °C; IR (KBr) υ_{max}/cm^{-1}; 3074 (CH aromatic), 2988 (CH aliphatic) and 2215 (C≡N); ^1H NMR (DMSO): 9.0 (s, 1H, quinoline H4), 7.9 (d, 1H, *J* = 9 Hz, quinoline H8), 7.5 (d, 1H, *J* = 9 Hz, quinoline H7), 7.4 (s, 1H, quinoline H5), 5.9 (m, 1H, CH alkene), 5.3 (d, 1H, *J* = 18 Hz, CH alkene), 5.1 (d, 1H, *J* = 11 Hz, CH alkene), 4.0 (d, 2H, *J* = 7.2 Hz, S-CH_2) and 3.9 (s, 3H,

OCH_3); MS (m/z, %); 256 (M, 61.25%), 241 (M – CH_3, 100%) and 200 (M – CN, OCH3, 26.9%); Anal. Calcd for $C_{14}H_{12}N_2OS$, (256): C, 65.60; H, 4.72; N, 10.93; O, 6.24; S, 12.51%. Found: C, 65.83; H, 4.81; N, 11.07%.

2.4.2. *6-Methoxy-2-(propylthio)quinoline-3-carbonitrile (**9b**)*
Yield (1.93 g, 75%); mp 105–106 °C; IR (KBr) υ_{max}/cm^{-1}; 3080 (CH aromatic), 2954 (CH aliphatic), 2220 (C≡N); ^{1}H NMR (DMSO): 9.0 (s, 1H, quinoline H4), 7.9 (d, 1H, *J* = 9 Hz, quinoline H8), 7.5 (d, 1H, *J* = 9 Hz, quinoline H7), 7.4 (s, 1H, quinoline H5), 3.8 (s, 3H, OCH_3), 3.4 (t, 2H, *J* = 7.2 Hz, SCH_2), 1.7 (m, 2H, CH_2), 1.1 (t, 3H, *J* = 16.2 Hz, CH_3); MS (m/z, %); 258 (M, 14.42%), 243 (M – CH_3, 5.4%), 229 (M – CH_3CH_2, 88%), and 83 (M –, 100%); Anal. Calcd for $C_{14}H_{14}N_2OS$, (258): C, 65.09; H, 5.46; N, 10.84%. Found: C, 65.21; H, 5.53; N, 11.01%.

2.4.3. *2-(benzylthio)-6-methoxyquinoline-3-carbonitrile (**9c**)*
Yield (2.60 g, 85%); mp 162–163 °C; IR (KBr) υ_{max}/cm^{-1}; 3042 (CH aromatic), 2850 (CH aliphatic), 2218 (C≡N); ^{1}H NMR (DMSO): 8.7 (s, 1H, quinoline H4), 7.9 (d, 1H, *J* = 9 Hz, quinoline H8), 7.6 (d, 1H, *J* = 9 Hz, quinoline H7), 7.5 (d, 2H, *J* = 6 Hz, phenyl H2, H6), 7.4 (s, 1H, quinoline H5), 7.3 (t, 2H, *J* = 6 Hz, phenyl H3, H5), 7.2 (t, 1H, phenyl H4), 4.6 (s, 2H, SCH_2), 3.8 (s, 3H, OCH_3).; MS (m/z, %); 306 (M, 31.71%), 215 (M – $C_6H_5CH_2$, 86%) and 91 (tropylium, 100%); Anal. Calcd for $C_{18}H_{14}N_2OS$, (306): C, 70.56; H, 4.61; N, 9.14%. Found: C, 70.73; H, 4.69; N, 9.31%.

2.4.4. *6-Methoxy-2-(phenethylthio)quinoline-3-carbonitrile (**9d**)*
Yield (2.72 g, 85%); mp 170–171 °C; IR (KBr) υ_{max}/cm^{-1}; 3080 (CH aromatic), 2901 (CH aliphatic), 2222 (C≡N); ^{1}H NMR (DMSO): 8.7 (s, 1H, quinoline H4), 7.9 (d, 1H, *J* = 9 Hz, quinoline H8), 7.6 (d, 1H, *J* = 9 Hz, quinoline H7), 7.5 (d, 2H, *J* = 6 Hz, phenyl H2, H6), 7.4 (s, 1H, quinoline H5), 7.3 (t, 2H, *J* = 6 Hz, phenyl H3, H5), 7.2 (m, 1H, phenyl H4), 3.9 (s, 3H, OCH_3), 3.5 (t, 2H, *J* = 15.3 Hz, S-CH_2), 3 (t, 2H, *J* = 15.3 Hz, CH_2Ph); Anal. Calcd for $C_{19}H_{16}N_2OS$, (320): C, 71.22; H, 5.03; N, 8.74%. Found: C, 71.35; H, 5.18; N, 8.95%.

3. Results and discussion

3.1. Chemistry

New 6-methoxyquinoline-3-carbonitrile derivatives were prepared through electrophilic substitution reaction of 2-mercapto-6-methoxyquinoline-3-carbonitrile with chloroacetanilides, alkyl chloroacetates and alkylhalides. The yield obtained by this method was almost more than 75%. Structure elucidation of amide derivatives **7a–f** was performed based on their spectral data (IR, ^{1}H NMR, and MS). The IR spectra of these compound showed the characteristic C=O absorption bands of amide at the range of 1655–1674 cm^{-1} while the C≡N bands were observed at the expected wavenumber in the range of 2220–2225 cm^{-1}. ^{1}H NMR spectra of the amide derivatives **7a–f** are characterized by the presence of D_2O exchangeable singlet of the NH proton at the range of 10.1–10.4 in addition to another singlet of three protons of methoxy group at 3.95 ppm. The singlet of methylene CH_2 bridge appears deshielded by the action of both the adjacent Sulfur atom and carbonyl group. Base peaks of the majority of these derivatives found almost at m/z 257 by loss of NH-aryl fragments. Structures of ester derivatives **8a–c** were confirmed by IR, ^{1}H NMR, and MS. There were C=O bands characteristic of ester at the range of 1731–1735 cm^{-1} in addition to the C≡N bands. The ^{1}H NMR spectra showed singlet of the methoxy group three protons at 3.95 ppm as well as signals due to different alkyl groups at the chemical shift of aliphatic region. Singlet of methylene CH_2 observed at 4.2–4.6 ppm. Furthermore, C≡N IR bands, OCH_3 signals were clearly detected in the spectra of all thioether derivatives **9a–d**. Compound **9c** revealed its base beak at m/z 91 due to tropylium carbocation. Detailed spectral data of all newly synthesized compounds were given in the experimental section.

3.2. Results of antimicrobial testing

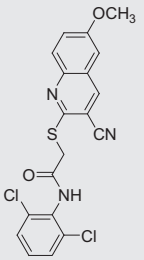
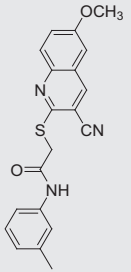
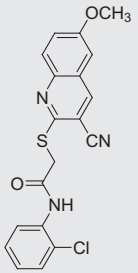
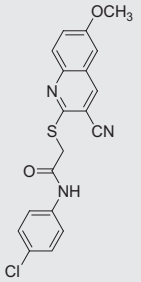
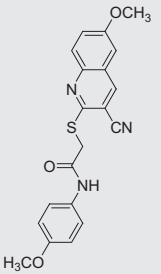
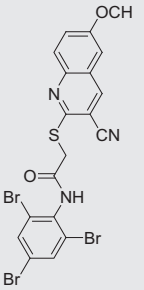
All of the newly synthesized derivatives were evaluated as antimicrobial against many Gram-positive and Gram-negative bacteria as well as many fungal strains. The results of antimicrobial evaluation showed promising activities for all of the test compounds. The in vitro antibacterial activity of newly synthesized derivatives was determined by disc diffusion method on nutrient agar (Bauer et al., 1966). In this work, two Gram-positive organisms (*Streptococcus pneumoniae*, *Bacillus subtilis*) and two Gram-negative organisms (*Pseudomonas aeruginosa*, and *Escherichia coli*) were used to investigate the antibacterial activity. The tested compounds were screened for their antifungal activity against *Aspergillus fumigatus*, *Syncephalastrum racemosum*, *Geotriucum candidum* and *Candida albicans* by poisoned food technique (Thembo et al., 2010). Bacterial and fungal strains were procured from the Regional Center for Micology and Biotechnology Laboratory, Cairo, Egypt. Ampicillin, Gentamicin and Amphotricin B were used as standards for antibacterial and antifungal studies respectively. The inhibition zones were recorded by visual observations after 24 h (bacteria) and 72–96 h (fungi) of incubation. Results of antimicrobial studies and the activity percent for each compound compared with the reference standard are presented in Tables 1, 2 and 3.

Screening procedure: The bacterial strain was uniformly spread using sterilecotton swab on a sterile Petri dish MH agar. 1 mg/mL for each test compounds were added to wells (7 mm diameter holes cut in the agar gel, 20 mm apart from one another). The systems were incubated for 24 h at 36 °C ± 1 °C, under aerobic conditions. After incubation, confluent bacterial growth was observed. Inhibition of the bacterial growth was measured in mm and compared to that of reference compounds.

4. Conclusion

From Tables 1, 2 and 3, it is clear that, the ester derivative 7b and the thioether derivative 9c showed the highest antimicrobial activity against gram-positive strains while the highest activity against gram-negative strains was observed in case of 7b, 7d and 9b. Compound 7e was found extremely potent against three of the selected fungal strains. No activity was found against *C. albicans* by any of the tested compounds. It can be expected that such compounds may exert their biological effects by more than one mechanism.

Table 1 – Results for antimicrobial activities of compounds 7a–f.

Comp. no.	7a	7b	7c	7d	7e	7f
Chemical structure						
I. Z. and % activity in *Streptococcus pneumoniae*	19.2 ± 0.55 80.6%	20.3 ± 0.37 85.29%	15.4 ± 0.19 64.71%	20.2 ± 0.19 84.87%	20 ± 0.43 84.03%	18.9 ± 0.44 79.41%
I. Z. and % activity in *Bacillus subtilis*	19.4 ± 0.52 59.88%	21.3 ± 0.25 65.74%	16 ± 0.58 49.38%	21.7 ± 0.24 66.9%	21.4 ± 0.53 66.04%	19.4 ± 0.53 59.88%
I. Z. and % activity in *Pseudomonas aeruginosa*	NA[a] 0.0%	NA 0.00%	NA 0.0%	NA 0.00%	NA 0.0%	NA 0.00%
I. Z. and % activity in *Escherichia coli*	18.9 ± 0.58 88.73%	20.6 ± 0.37 96.71%	13.5 ± 0.44 63.38%	22.1 ± 0.24 103.76%	16.3 ± 0.33 76.53%	16.4 ± 0.23 77.0%
I. Z. and % activity in *Aspergillus fumigatus*	18.6 ± 0.36 78.48%	17.8 ± 0.36 75.11%	15.4 ± 0.44 64.98%	19.8 ± 0.44 83.54%	18.3 ± 0.34 77.22%	15.6 ± 0.53 65.82%
I. Z. and % activity in *Syncephalastrum racemosum*	17.3 ± 0.35 87.82%	18.3 ± 0.35 92.89%	14.6 ± 0.25 74.11%	18.7 ± 0.24 94.92%	21.1 ± 0.25 107.11%	12.7 ± 0.36 64.47%
I. Z. and % activity in *Geotriucum candidum*	16.5 ± 0.44 57.49%	14.9 ± 0.58 51.92%	13.1 ± 0.58 45.64%	17.3 ± 0.28 60.28%	21.3 ± 0.38 74.22%	16.3 ± 0.44 56.79%
I. Z. and % activity in *Candida albicans*	NA 0.00%	NA 0.00%	NA 0.00%	NA 0.00%	NA 0.00%	NA 0.00%

I. Z. = Inhibition zone.
[a] No activity.

Table 2 – Results for antimicrobial activities of compounds 8a–C.

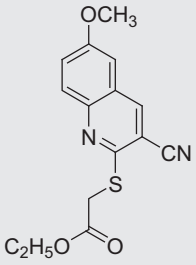
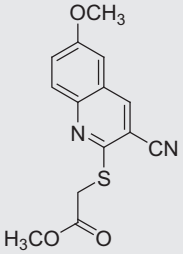
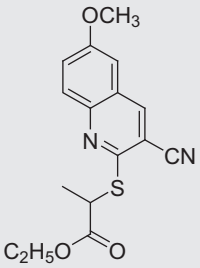
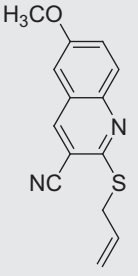
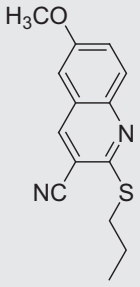
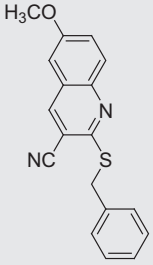
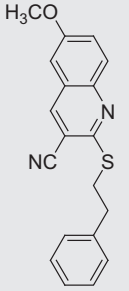
Comp. no.	8a	8b	8c
Chemical structure			
I. Z. and % activity in *Streptococcus pneumoniae*	10.6 ± 0.34 44.54%	15.9 ± 0.25 66.81%	17.7 ± 0.43 74.37%
I. Z. and % activity in *Bacillus subtilis*	13.7 ± 0.25 42.28%	17.1 ± 0.63 52.78%	19.3 ± 0.53 59.57%
I. Z. and % activity in *Pseudomonas aeruginosa*	NA 0.00%	NA 0.00%	NA 0.00%
I. Z. and % activity in *Escherichia coli*	8.3 ± 0.58 38.97%	10.3 ± 0.44 48.36%	13.7 ± 0.25 64.32%
I. Z. and % activity in *Aspergillus fumigatus*	10.6 ± 0.25 44.73%	15.9 ± 0.25 67.09%	17.6 ± 0.58 74.26%
I. Z. and % activity in *Syncephalastrum racemosum*	11.1 ± 0.27 56.35%	16.1 ± 0.44 81.73%	19.4 ± 0.25 98.48%
I. Z. and % activity in *Geotriucum candidum*	11.9 ± 0.35 41.46%	19.2 ± 0.63 66.9%	19.9 ± 0.38 69.34%
I. Z. and % activity in *Candida albicans*	NA 0.00%	NA 0.00%	NA 0.00%

Table 3 – Results for antimicrobial activities of compounds 9a–d.

Comp. no.	9a	9b	9c	9d
Chemical structure				
I. Z. and % activity in *Streptococcus pneumoniae*	18.9 ± 0.44 79.41%	17.9 ± 0.37 75.21%	20.3 ± 0.43 85.29%	16.9 ± 0.44 71%
I. Z. and % activity in *Bacillus subtilis*	20.3 ± 0.58 62.65%	18.5 ± 0.28 57.1%	21.4 ± 0.53 66.05%	19.3 ± 0.25 59.57%
I. Z. and % activity in *Pseudomonas aeruginosa*	NA 0.00%	NA 0.00%	NA 0.00%	NA 0.00%
I. Z. and % activity in *Escherichia coli*	18.9 ± 0.63 88.73%	19.1 ± 0.44 89.67%	16.9 ± 0.25 79.34%	14.9 ± 0.44 69.95%
I. Z. and % activity in *Aspergillus fumigatus*	16.3 ± 0.44 68.78%	15.7 ± 0.19 66.24%	17.6 ± 0.58 74.26%	15.6 ± 0.44 65.82%
I. Z. and % activity in *Syncephalastrum racemosum*	18.4 ± 0.58 93.4%	13.8 ± 0.19 70.05%	18.2 ± 0.25 92.39%	16.2 ± 0.58 82.23%
I. Z. and % activity in *Geotriucum candidum*	19.1 ± 0.37 66.55%	16.9 ± 0.37 58.89%	20.3 ± 0.38 70.73%	17.9 ± 0.37 62.37%
I. Z. and % activity in *Candida albicans*	NA 0.00%	NA 0.00%	NA 0.00%	NA 0.00%

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